1/1 ページ

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(54) POLYSULFONE HOLLOW FIBER MEMBRANE AND ITS PRODUCTION

(57)Abstract:
PURPOSE: To prepare a membrane excellent in anti-thrombus property and adaptability for blood with which blood protein of high mol.wt. can be removed by constituting the hollow fiber membrane of a polysulfone resin and a hydrophilic polymer and forming a dense active layer in the inner surface side of the membrane and forming pores having specified properties in the outer surface side.
CONSTITUTION: This hollow fiber membrane consists of a polysulfone resin and a hydrophilic polymer such as polyvinylpyrolidone. The hollow fiber membrane has a dense active layer in the inner surface side and has pores of 0.3-20μm average pore diameter in the outer surface side. The membrane has such properties that the porosity on the outer surface is 20-50%, the inside of the membrane contains no microvoid of ≥5μm size, the screening coefft. for albumen albumin is ≥0.2, and water permeability is 100 to 500ml/ hr.m2.mmHg. This hollow fiber membrane has low permeability for albumin although protein in 20000-40000mol.wt. range can be removed with this membrane.

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CLAIMS

[Claim(s)]
[Claim 1] It is the polysulfone system hollow fiber which is a hollow fiber which consists of polysulfone system resin and a hydrophilic macromolecule, has an average apertures [0.3-2.0micro] hole for a barrier layer precise to the internal-surface side of this hollow fiber in an outside-surface side again, the hole density of the hole in this outside surface is 20 - 50%, does not have a macro void 5micro or more inside the film, but is characterized by for the sieve multiplier of ovalbumin being 0.2 or more, and the amounts of water penetration being 100 - 500 ml/hr-m2 and mmHg.
[Claim 2] The polysulfone system hollow fiber according to claim 1 characterized by hydrophilic giant molecules being a polyvinyl pyrrolidone and/or a polyethylene glycol.
[Claim 3] The polysulfone system hollow fiber according to claim 1 or 2 characterized by the content of the hydrophilic macromolecule which exists in this polysulfone system hollow fiber being 3 - 20%.
[Claim 4] The manufacture approach of the polysulfone system hollow fiber characterized by making absolute humidity of the air transit section into 0.02-0.3kg and water / kg, and dry air in the approach of manufacturing a hollow fiber with dryness-and-moisture type spinning, using the film production undiluted solution which dissolved polysulfone system resin, a hydrophilic macromolecule, and these in the homogeneity which consists of a solvent in which it is made to dissolve in common.
[Claim 5] The manufacture approach of the polysulfone system hollow fiber according to claim 4 characterized by hydrophilic giant molecules being a polyvinyl pyrrolidone and/or a polyethylene glycol.

[Claim 6] The manufacture approach of the polysulfone system hollow fiber according to claim 4 or 5 characterized by the temperature of the air transit section being 25-60 degrees C.
[Claim 7] A polysulfone system hollow fiber given in either of claims 1, 2, and 3 characterized by producing a film by the approach of a publication to either of claims 4, 5, and 6.

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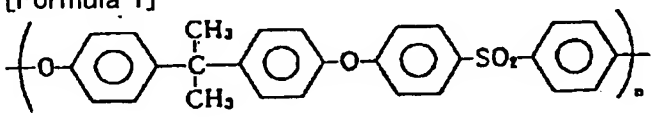
DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the hollow fiber for hemodialysis used suitable for especially medical application, and its process about a polysulfone system hollow fiber.
[0002]
[Description of the Prior Art] Although the artificial kidney of current various kinds is used for the therapy of renal failure, these aim at performing hemodialysis and hemofiltration using a hollow fiber and removing the wastes in blood, such as a urea. Therefore, in order that blood may contact the film, a safe material must be used to a living body, for example, a cellulose, cellulose acetate, a polyacrylonitrile, polymethylmethacrylate, a methylene-vinyl alcohol copolymer, etc. have been used widely until now. Moreover, recently, the hollow fiber which used polysulfone as main material attracts attention, and the technical indication is made by JP,2-18695,B, JP,5-54373,B, and JP,3-267128,B.
[0003] However, the film of said official report is inadequate for considering as the film for hemodialysis, for example, since in the case of the hollow fiber of the indication to JP,2-18695,B fixing between hollow fibers is intense, and a module cannot be cast or a cut off molecular weight does not spread the film of the indication to JP,5-54373,B by 3000 to 40,000, it cannot but be the dissatisfied film to remove the protein of the molecular weight field of 20,000-40,000 in the present condition of the dialysis treatment technique currently searched for. Moreover, since the amount of water penetration is high and an aperture is also too large, the film of the indication to JP,3-267128,B cannot be used as film for hemodialysis any longer.
[0004]
[Problem(s) to be Solved by the Invention] This invention is excellent in anti-thrombus nature and haemocompatibility, offers the polysulfone system hollow fiber for artificial kidneys which can remove the blood protein of the amount of macromolecules further, and contributes to improvement in hemodialysis treatment technique.
[0005]
[Means for Solving the Problem] It has anti-thrombus nature and haemocompatibility, and in order to offer the large polysulfone system hollow fiber of a cut off molecular weight, this invention persons come to complete this invention wholeheartedly as a result of examination. Namely, it is the hollow fiber which consists of polysulfone system resin and a hydrophilic macromolecule. In an outside-surface side, it has an average apertures [0.3-2.0micro] hole for a barrier layer precise to the internal-surface side of this hollow fiber again. The hole density of the hole in this outside surface is 20 - 50%, and it does not have a macro void 5micro or more inside the film. It is the polysulfone system hollow fiber characterized by for the sieve multiplier of ovalbumin being 0.2 or more, and the amounts of water penetration being 100 - 500 ml/hr-m2 and mmHg, and this invention is explained below at a detail.
[0006] Although polysulfone system resin is especially the generic name of the high molecular compound which has sulfone association and it does not specify, when an example is given, the polysulfone resin shown by following the (1) type or (2) formulas is marketed widely, since acquisition is also easy, it is desirable, and polysulfone resin with the chemical structure shown by (1) formula especially is good. The polysulfone resin with this structure is marketed by the brand name of "you

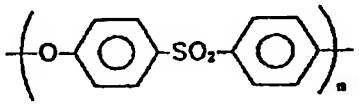
Dell" from the Amoco performance products, and especially although some classes exist with polymerization degree etc., it is not scrupulous.

[0007]

[Formula 1]



..... (1)



..... (2)

[0008] Moreover, although the giant molecule which has the hydrophilic property of a polyvinyl pyrrolidone, a polyethylene glycol, polyethyleneimine, polyacrylic acid, etc. as a hydrophilic giant molecule can be used, since the compatibility over polysulfone system resin is good, a polyvinyl pyrrolidone and a polyethylene glycol are used preferably and a polyvinyl pyrrolidone is used most preferably especially.

[0009] The dryness-and-moisture type film production technique which is a technique generally known from before on the occasion of film production of the hollow fiber in this invention can be used, and the polymer solution which dissolved in the homogeneity which consists of polysulfone system resin, a hydrophilic macromolecule, a solvent, and/or nonsolvent as a film production undiluted solution for performing dryness-and-moisture type film production is used.

[0010] For creating this film production undiluted solution, the solvent which has solubility in common to both polysulfone system resin and hydrophilic macromolecule is used, and although it does not specify especially, if an example is given, the solubility of solvents, such as N,N-dimethylacetamide, N, and N-dimethyl formamide, N-methyl pyrrolidone, and dimethyl sulfoxide, is also expensive, and since acquisition is also easy, it will be used suitably. N,N-dimethylacetamide and N-methyl pyrrolidone are good from the safety to the soluble height and living body to polysulfone etc. especially, and N,N-dimethylacetamide is used most preferably especially. Moreover, it is not necessary to use these solvents independently, and they can also mix and use two sorts or the solvent beyond it with the purpose of adjusting the solubility over a polymer and adjusting the viscosity of a film production undiluted solution. It is also possible to add nonsolvents, such as glycols, such as mineral, such as alcohols, such as water, and isopropyl alcohol, ethanol, a sodium chloride, and a calcium chloride, propylene glycol, and tetraethylene glycol, furthermore, and it becomes an advantageous approach in order to control membraneous ability, since the shape of membranous is changeable by carrying out like this. What is necessary is just to choose suitably according to the description of the hollow fiber made into the purpose about the addition and a class.

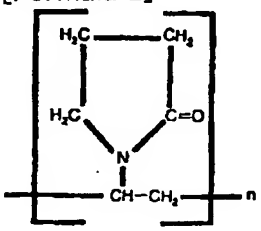
[0011] Since membranous formation will become difficult if too few, film reinforcement becomes weak too much or phenomena, like an aperture will worsen [spinning nature] too much small if many [too] arise, as for the addition of this polysulfone system resin, it is desirable that it is 16 - 18 % of the weight especially 15 to 20% of the weight. However, what is necessary is it not to be absolute that it is this range, and to be also able to enlarge making it smaller than this range depending on the description of the hollow fiber made into the purpose, and just to choose the optimal combination suitably, since the shape of membranous changes also by changing other spinning conditions. Although the high molecular compound which has the hydrophilic property of a polyvinyl pyrrolidone, a polyethylene glycol, polyethyleneimine, polyacrylic acid, etc. as this hydrophilic giant molecule is used, there is no need of not necessarily using it independently, can mix several sorts of hydrophilic giant molecules, and can also be added.

[0012] The addition of the hydrophilic macromolecule to a film production undiluted solution does not generally have **********, in order that the optimal addition field may change depending on the class of hydrophilic macromolecule, or the molecular weight of a hydrophilic macromolecule, but when it is generally 3 - 30% and a hydrophilic macromolecule is a polyvinyl pyrrolidone, 3 - 20 % of the weight is 3 - 15 % of the weight desirable still more preferably. A polyvinyl pyrrolidone is a water-soluble high

molecular compound which has the structure of following the (3) type, is the trademark of a "plus boss" from insertion sequence Py, and is marketed with the trademark of "Kollidon" from BASF, and has the polyvinyl pyrrolidone of some molecular weight, respectively.

[0013]

[Formula 2]



..... (3)

[0014] Since the purpose which adds a hydrophilic macromolecule to a film production undiluted solution is making a hydrophilic macromolecule remain in a hollow fiber, and giving a hydrophilic property to the film, selection of the molecular weight is very important. It is because this hydrophilic macromolecule comes out out of the film easily at the time of the coagulation of a film production undiluted solution, and washing of the obtained hollow fiber, so a lot of hydrophilic macromolecules must be added to a film production undiluted solution in order to make enough hydrophilic macromolecules to give a hydrophilic property to a hollow fiber remain in a hollow fiber if the molecular weight of a hydrophilic macromolecule is too small. Therefore, in order to raise the survival rate to the inside of the hollow fiber of a hydrophilic macromolecule, the larger one of molecular weight is good, and since it can utilize effectively and the hydrophilic macromolecule added to the film production undiluted solution by that can lessen an addition, it is desirable.

[0015] Also when a hydrophilic giant molecule is a polyvinyl pyrrolidone, the larger one of molecular weight is desirable, for example, when using the polyvinyl pyrrolidone which has 500,000 or more viscosity average molecular weight, it is good that it is 3 - 6 % of the weight. What is necessary is just to do as the back volume made to immerse and solidify into the coagulation bath which makes a subject the water installed in the spinning port lower part, after extruding the liquid in hollow for facing producing a hollow fiber and making a film production undiluted solution and this film production undiluted solution solidify from this spinning port using the duplex spinning port of a tube in orifice mold in the air to coincidence and making it run the 20-50cm free-running section.

[0016] The important thing at this time is producing a film in the condition of especially becoming 3,500 to 5,000 centipoise, 1,500 to 6,000 centipoise in the viscosity of this film production undiluted solution. What is necessary is to warm or just to cool the viscosity of a polymer solution, in order to press down the viscosity of a film production undiluted solution within the limits of this although changing with that presentation, temperature, etc. is known well. Namely, what is necessary is it to be important for the bottom of a film production condition not the viscosity in the conditions uniformly specified as the viscosity said here but to control undiluted solution viscosity in short, and just to set up condition range where this viscosity serves as 1,500 to 6,000 centipoise.

[0017] Although it does not understand well about the reason, if viscosity produces a hollow fiber using the film production undiluted solution of a low condition, a bigger macro void than 5micro will come to appear notably inside the film, but when many such macro voids existed in the case of the hollow fiber for hemodialysis, and activation of the platelet in blood becomes intense and it considers as an artificial kidney, a stable hemodialysis therapy will become impossible. Therefore, it is desirable that there is no macro void in the hollow fiber used for hemodialysis, and it is desirable that undiluted solution viscosity produces a film in the condition of 1,500 or more centipoises for that purpose. As for a macro void here, the overall diameter says a thing 5micro or more among the hole sections in which a polymer does not exist inside the film. On the other hand, since spinning nature will worsen and thread breakage etc. will occur frequently if undiluted solution viscosity becomes high too much, it is good to use the undiluted solution of the viscosity condition which does not exceed 6,000 centipoises.

[0018] The ambient atmosphere of the free-running section is still more important, and it is making into 0.02 - 0.3 kg-H2 O/kg and dry air absolute humidity of the ambient atmosphere the hollow fiber which was extruded from the duplex spinning port and began coagulation runs. By setting the humidity

ambient atmosphere of the free-running section as the humidity condition of this range, it becomes possible to be able to make high hole density of the outside surface of a hollow fiber, and to prevent fixing between hollow fibers, and big effectiveness is demonstrated to raising the moldability to a module.

[0019] Although it does not understand in detail about the reason, the steam of the free-running section contacts to the outside surface of the film production undiluted solution of the shape of a hollow filament breathed out from the duplex spinning port, and the coagulation of a film production undiluted solution is induced, and by the time coagulation is completely completed in a coagulation bath, it will also set, and coagulation advances gently. Consequently, since it is immersed in the condition in which phase separation advanced in the outside surface of the film production undiluted solution of the shape of a hollow filament breathed out from the spinning port, i.e., the condition of having separated into the polymer high concentration phase and the polymer low concentration phase, into a coagulation bath and coagulation is completed, it is thought that a polymer low concentration phase becomes a hole. Although it is good to consider as 0.04 - 0.20 kg-H2 O/kg and dry air still more preferably, in order to carry out high humidity, the free-running section is intercepted with the external world with a hood etc., and saturated steam can be blown into the this intercepted hood, or it can attain by making full in a hood etc. the steam generated by raising the temperature of a coagulation bath.

[0020] The liquid in hollow can use the coagulation liquid which made water or water the subject, and although there is no ********** generally that what is necessary is just to decide the presentation etc. suitably according to the membraneous ability of the hollow fiber made into the purpose, the mixed solution of the solvent and water which were generally used for creation of a film production undiluted solution is used suitably. For example, although 20 - 60% of the weight of a N,N-dimethylacetamide water solution etc. is used, 35 - 50 % of the weight is especially good. Moreover, a hydrophilic macromolecule water solution can also be used for this liquid in hollow. It rolls round after washing, and aperture hold-back agents, such as a glycerol and a polyethylene glycol, can be made to be able to give if needed, it can back-dry, and the produced hollow fiber can be obtained as desiccation film.

[0021] The hollow fiber obtained by this invention had the hole of magnitude (0.3-2.0micro) by 20 - 50% of hole density in the membranous outside-surface side, having the compact layer in the membranous internal surface. the hollow fiber which has a precise layer in an outside-surface side -- or it has semantics with the big structure of an outside surface at the point which makes easy enclosure according [although it does not understand well about the reason from enclosure by the potting material when fixing between hollow fibers being intense when it is a hollow fiber with hole density small in a hole being small even if puncturing is seen, and casting an artificial-kidney module having been inadequate, prevent fixing of a hollow fiber, and] to potting material.

[0022] On the other hand, since the permeability of protein will become high too much and it not only becomes the hollow filament which the reinforcement of a hollow fiber becomes weak and is hard to deal with it, but it will become unsuitable as a hollow fiber for hemodialysis if a film aperture is larger than 2.0micro and hole density becomes large from 50%, it is not desirable. After the magnitude of a hole here asks for the puncturing area of each hole by the image processing, the diameter which considered that this area was a circle and converted it is said, and an average aperture means the aperture which carried out the arithmetic mean to the magnitude of each hole from that number. namely, the aperture of the hole of N individual -- respectively -- D1, D2, and ... when referred to as DN, an average aperture is computed by the following (4) formulas. Moreover, hole density is expressed as total of the puncturing area of the one-piece one hole which exists in an unit area.

Average aperture = (D1+D2+ ... +DN) /N ..... (4)

Moreover, since the cut off molecular weight is enlarged with about 50,000, by the usual hemodialysis film, as for the hollow fiber obtained by this invention, removal even of the unnecessary protein of large molecular weight with difficult removal is attained.

[0023] In spite of having the big hole (0.3-2.0micro) in the outside surface in the case of the hollow fiber by this invention Since the precise barrier layer is given to the internal surface, the permeability of the albumin in blood to the total protein in blood is 5% or less. And since it became possible to make the matter of comparatively big molecular weight like ovalbumin penetrate by controlling coagulation

conditions appropriately Removal of the unnecessary protein which has the molecular weight of 20,000-40,000 in blood can be performed, when preventing the various complication accompanying long-term dialysis, big effectiveness can be demonstrated, and a big contribution is carried out to improvement in the dialysis iatrotechnique. In addition, as for this invention, it is needless to say only as a film material of medical application, such as hemodialysis, that you may use it as film of various kinds of industrial use.

[0024]

[Example] An example and the example of reference are used for below, and this invention is explained to it at a detail.

(Example 1) The uniform film production undiluted solution which consists of the polysulfone resin (Amoco performance products, P-1700) 18 section, the polyvinyl-pyrrolidone (insertion sequence Py, K-90) 5 section, and the N,N-dimethylacetamide 77 section was created. In order to use 40% of the weight of a N,N-dimethylacetamide water solution as the liquid in hollow, to extrude said film production undiluted solution from a duplex spinning port to coincidence as a 45-degree C condition (3,800 centipoises) and to intercept from the external world, it was immersed in underwater [which was prepared / be / it / under / of the hood attached / for / passing / caudad 30cm / 50-degree C], and rolled round at the rate of 50 m/min. At this time, when the inside of a hood has high humidity for the steam from a coagulation bath and surveyed absolute humidity, it was 0.05 kg-H2 O/kg and dry air. After processing the obtained hollow fiber in 20% of the weight of a glycerol water solution, it evaluated by drying at 75 degrees C. The average aperture of the outside surface of this film was 1.1micro, and hole density was 35%.

[0025] (Example 1 of reference) Spinning was performed on the same conditions as an example 1 except having removed the hood of the free-running section. The absolute humidity of the free-running section at this time was 0.016 kg-H2 O/kg and dry air. The same processing as an example 1 was performed, and the hollow fiber was dried. They were 0.2micro of average apertures of an outside surface, and the hollow fiber of 16% of hole density.

[0026] (Example 2) 9,500 hollow fibers obtained in the example 1 were inserted in the cylindrical resin case, and potting of the polyurethane was carried out by 750 rotations by the centrifugal casting method. Polyurethane was what is enclosed between hollow fibers, can cast satisfactory and can also satisfy yield.

(Example 2 of reference) Although centrifugal molding was performed on the same conditions as an example 2 except using the hollow fiber obtained in the example 1 of reference, polyurethane was not enclosed between hollow fibers, but yield was very low. Molding yield was shown in Table 1.

[0027]

[Table 1]

表 1

膜　　種	実施例 1	参考例 1
内径／膜圧（μ）	205／43	202／44
収　率　（%）	92	56

[0028] (Example 3) The mini module (25cm of effective length) which consists of 100 hollow fibers obtained in the example 1 was created, and the amount of water penetration was measured by the stopping method also as that of the flow and pressure requirement of 200mmHg. Then, the 250 ppm water solution of ovalbumin was dipped in the mini module, and the sieve multiplier of ovalbumin was measured. In addition, an ovalbumin sieve multiplier is the value computed using the following (5) types from the ovalbumin concentration in the former liquid measured by 280nm, and the ovalbumin concentration in filtrate.

Sieve multiplier = ovalbumin concentration of the ovalbumin concentration / former liquid of filtrate ...

(5)
The measurement result was shown in Table 2.
[0029] (Example 3 of reference) Except using the hollow fiber obtained in the example 1 of reference, the mini module was created like the example 3 and measurement of the amount of water penetration and an ovalbumin sieve multiplier was performed. The measurement result was shown in Table 2.
[0030]
[Table 2]
表2

膜　種	実施例1	実施例2	実施例3
透水量	320	180	85
篩い係数	0.6	0.3	0.1

透水量　ml／hr・m2・mmHg

[0031] (Example 4) The same mini module as an example 3 was created using the hollow fiber of an example 1. the place which filtered dipping cow plasma (total protein concentration of 5.5g) under the pressure of 200mmHg(s), and saw the transmission of the albumin to total protein -- 0.9% and a pole -- it was small and was the level which is satisfactory practically.
[0032]
[Effect of the Invention] In spite of attaining the protein removal of the molecular weight field of 20,000-40,000 of molecular weight according to the hollow fiber of this invention, since permeability of albumin is low, the practical thing which can be used satisfactory is clear, and a very significant artificial kidney can be offered in the future dialysis treatment asked for protein removal of the amount of macromolecules.

[Translation done.]